

## LABORATOIRE DE GÉNÉTIQUE

13, RUE PIERRE CURIE, PARIS V'

TÉL. : ODÉON 16-40

January 5, 1950

Dear Joshua,

I am sorry to be so slow in answering your letter, with its many queries. Being so late permits me to wish you a good new year, which I do gladly.

I shall proceed first to the business of replying to some of the points which you raised in your lengthy letter. First of all, about the introductory remarks in my JEM paper; I do not believe that there is any adequate evidence which proves that bacteria have genetic systems comparable to those of higher organisms. What you consider as conclusive proof, I find inadequate as proof. In fact, I believe it is wishful thinking, to go so far as you do. I think you are too eager, as a result of your work on E. coli, to accept the evidence which you cited to me, in support of your position with regard to your own experiments. Let us examine the case of the antigens which may be digested off of the bacteria with enzymes. It is something with which I am familiar, and can see the limitations of it as support for your convictions about its significance. Enzymatic treatment does not destroy the power of the bacterium to reform its surface structure. Never, enzymatic treatment does not destroy, either, the capacity of these bacteria to induce antibodies against the cellular components which were supposedly removed by the treatment. The conclusion of this, is, I think, that not all of these antigens is removed by the enzymatic treatment. Thus, at no point do you have bacteria capable of synthesizing these antigens, and yet which are lacking these antigens. It should be added that even when the enzymatic treatment is carried out on dead bacteria, not all of the antigen can be removed, and hence the traces which are presumably left cannot be due to a rapid resynthesis after removal of the enzyme. I do not believe that this evidence indicates at all the separateness of the antigen from the genetic mechanism which determines its presence. This criticism certainly applies in the case of the polysaccharide antigen of pneumococcus. If it is found that streptococci treated with proteolytic enzymes lose ~~really~~ the M antigen, it should be added that the M antigen is a poor one, and one must not overlook the possibility that the apparent absence of the antigen after enzymatic treatment is due to the small amount which is left. As for the flagella which can be shaken off, and which regenerate, again one must be very reserved. Are they totally removed, or are they simply broken off at their base? If they are broken off at the base, does this mean that the gene and the flagellar substance are really separate things? As to adaptive enzymes, again, are they totally absent in the bacterium, or present only in reduced amounts? or present as precursors? There are interpretations of all of these phenomenon other than the one you propose, which might be invoked to explain the results observed. Thus, one cannot call this kind of evidence unequivocal. As to giving the bacteriologists consolation for their resistance to the new ideas introduced by geneticists, the point doesn't interest me. I am interested in trying to be objective about the present state of the questions involved, and in my introduction I have expressed how it adds up for me at present. The geneticists in bacteriological work are behaving in an unscientific fashion, on the whole, because they seem to feel that they have to fight the reactionary views of bacteriologists. Such an attitude is fine for politics, but poor for science. However right gene-

## LABORATOIRE DE GÉNÉTIQUE

13, RUE PIERRE CURIE, PARIS V'

TÉL. : ODÉON 16-40

neticists may be at the moment in their various contentions about bacterial heredity their data <sup>is</sup> ~~is~~ not sufficient at the moment to make a tight case for their arguments. When these data are good enough, there will be no trouble in having these views accepted

Naturally I am delighted that you were sufficiently interested in my experiments to read them in detail. You ask whether it is necessary to invoke "interaction" to explain the results of certain transformations. I am not prepared to say very much about that yet, since it is the subject on which I am working at present. For the moment it looks as though I shall have to explain these particular transformations as interactions between a TP in the bacterium already, and one introduced from the environment. We shall see, ~~though~~, I hope, whether this is the case, before so very long. I agree that the existence of this interaction is difficult to reconcile with the notion of allelism. But you will notice that the only aspect of allelism which I want to borrow from genetics at the moment is the notion that alleles are derived by mutation from one <sup>a given gene</sup> and the same genetic determinant. The fact that one never observes interaction -- i.e. what Lindegren calls contamination, if I remember correctly -- in heterozygotes may be very well due to the orderly fashion in which chromosomes reproduce themselves. Genetically active substances, comparable to our TP, may never be so misplaced in higher organisms as to interfere with the purity of each gene.

Now as to the inhibition by antiserum. This is a phenomenon which I "rediscovered", since it had been more or less forgotten that <sup>type</sup> specific antibody inhibits transformations of R to S. I don't see what unpublished experiments you want me to publish on the subject. Is a table any more convincing than the statement that you cannot get transformations in the presence of specific antibody, in transformations of R to SIII? You may know that editors get very fussy if you give them too many tables. Actually it is a relatively unimportant part of the proof that rare R mutants of the SIII-1 strain cannot be responsible for the transformations of this strain to SIII-N. If you regard the titrations published, you will see that it takes less transforming principle to transform the SIII-1 bacteria to SIII-N than it does to transform R to SIII-N. Such titrations could not be obtained if the SIII-1 to SIII-N transformation depended upon the formation of a rare spontaneous R mutant in the population. It is simply impossible. If MacLeod had been able to do in vitro transformations with his SII mutant, and show the same quantitative relations, I should never have criticised his conclusions. As to your suggestion that the SIII-1 bacteria can adsorb out all of the Type specific antibody, and thereby permit the transformation of rare R mutants, it isn't really to be seriously considered, because you can transform SIII-1 to SIII-N in the presence of large amounts of Type III antibody, in which both seeded cells and transformed progeny stay agglutinated. It works very well, in fact. Furthermore, returning to the possible role of R mutants in this transformation, one would have to suppose that these mutants are frequent enough so that always after 4-5 hours' growth sufficient of them are present and in the sensitized state to react with the TP within as short a time interval as 5 minutes. You just can't get this sort of results if your transformation is based upon the effective encounter of a rare R mutant with the TP, which is not present in very great concentration either. *And you cannot find R mutants with any measurable frequency in the SIII-1 stock.*

Now as to interpretation of the reciprocal transformations. You are welcome to make any hypothesis which pleases you. I have only presented one which I feel is plausible. As to the ingenious theory which you

propose, I think that you have neglected the fact that the ER TP, like the R TP seems to be a desoxyribonucleic acid. If it were a protein, I should feel quite differently about your theory. Both entities being composed of the same chemical substance, I feel that they are probably attached in the cell to the same kind of substance -- probably a protein, and perhaps even the same protein.

You suggest an <sup>experiment</sup> ~~hypothesis~~ to test your theory of the ER to R, R to ER transformations. It follows very well from your hypothesis, according to which one should try to see if the ER principle competes with the R bacterium for the R principle. While this experiment is feasible, I shouldn't know how to interpret the results it might bring. Most certainly one would observe a diminution in the power of the R transforming principle to transform ER. But in which sense is the competition taking place? One might also interpret it as meaning that both ER TP and R TP, in the environment, are competing for the same receptor in the ER bacterium. DNA preparations which are inactive in transformations do inhibit the action of the SIII transforming principle, and presumably because there is competition somewhere in the transforming mechanism -- competition between the active and inactive DNA. It is possible that the sensitized cell gets "saturated" with inactive DNA molecules, and that the active ones have too little chance for reacting with the sensitized pneumococci. You see, it is not so simple.

You speak of competition between transforming principles. I agree that there is reason to wonder if the term might not apply in some cases. However, I am loathe to borrow the term. I do not believe that one gains in clarity by borrowing a term from a discipline, where it has a well defined meaning, and using this term for a phenomenon which may be entirely unrelated.

Competition has been taken from enzyme chemistry by the workers in vitamin research, for dealing with vitamin analogues. This may be justified, for the quantitative results of the vitamin work would support this. But there is a very big difference between the substrates and the vitamins and the analogues of enzyme chemistry and vitamin research, and our TP molecules. The former are small molecules, which may be supposed to obey the established kinetic laws, but the latter are not. I don't imagine that ordinary kinetics, which depends so much on thermal agitation, fits molecules of the dimensions of the TPs. Superficially, the transformation in question might suggest a competition for a locus in the bacterium, and differences in affinities, but I am inclined to believe that to label it such may be unjustified. Perhaps it even obscures some very interesting aspects of the phenomenon.

I see in glancing up at what I have just written that I have already confused two notions of "competition". In the next to the top paragraph, the "competition" is not the same as that referred to in the paragraph just preceding. In the one case, one really means interference, and in the second one means competitive inhibition, and these are not really the same thing. Interference may not be due to competitive inhibition. How easy it is to go astray.

As to Macleod and Austrian's transformations, I would like to know myself whether or not they are the same as the ER to R transformations. I am too busy to anything about it myself.

Now turning briefly to the question of cytoplasmic hereditary units. For the moment there is so little to go on, I don't think it worth speculating at any length as to whether the transformations are cytoplasmic or not. As far as I can see, most bacterial mutation phenomena can be interpreted equally well as cytoplasmic or nuclear events, since as far as I know, there has been no real correlation demonstrated between nuclear events and genetic events. Indeed, it is not possible to imagine that some of the phenomena you describe are cytoplasmic? For example, how can you be sure that the "block of genes" which are systematically lost together in kl2 are not on a cytoplasmic granule which gets lost fairly frequently

ng division?

As to the number of characters which may be present in the TP, as far as I am concerned, the more the better. It only tends to show that what we are studying is not so esoteric.

I do find two things disturbing in your papers and letter. One is the urge you have to make a uniform picture of genetic systems in bacteria and higher organisms. I don't think you have been skeptical enough in print of your own interpretations. Now the recombination phenomenon you describe is becoming alarmingly complicated, and one is wondering whether the events really are at all like the hybridizations found in higher plants and animals. Perhaps the complications are a fortunate event; certainly so, if it compels you to reexamine the basic supposition that you are dealing with a real hybridization. Perhaps it was unfortunate that you happened onto such exciting material so young in life. Who knows, maybe if you had been 15 years older you would not have tried to force your discoveries into a conventional mould. The second disturbing thing is really an outgrowth of the first. It is an excessive rationalizing about things. There is nothing which can replace experiments. One has the feeling that you are so impatient to construct a unified picture of heredity -- identify your work with the great trends of genetics -- that you cannot wait to perform experiments, but must construct the system on slender evidence and tremendous rationalization. Just think how much more exciting it would have been to discover a totally new kind of mechanism for genetic recombination! Hybridization is an old stick! You are a strange combination of urges, if you will forgive my saying so. The urge to find something new, crippled by the urge to force the new into an old pattern. I have enough of this mixture myself to have some feeling for what it is.

Things are fine here on the whole. Our new institute is going to be ready for us to move in next fall, if all goes well. We are very eager for the move, since we are terribly crowded. It should be really very nice. I shall have some very much needed facilities, which are going to simplify my work considerably. A sterilizable sharples' centrifuge, and more adequate constant temperature rooms. We shall have very comfortable labs. Not luxuriously beautiful, but very adequate.

We hope very much to come to the States next fall, for the New Haven congress. Money is very much a question, still. The French cannot do much in the way of supporting a trip, and we are still waiting to hear if the congress is going to live up to its invitation financially. All depends on that. We shall certainly come through Madison, where I have relatives, and where we shall want to visit in any case. So if you are not at the congress, we shall probably see you anyway, if you are going to be in Madison from the end of September on.

Well, really this is enough to write at one time!

With best wishes to both you and Esther. I am glad to hear she has done so well with her work. It is very nice to live with someone who understands what it is all about, isn't it?

Sincerely,

*Harriet*